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GRANT NUMBER DAMD17-94-J-4029

TITLE: New Approaches to the Labeling of Estrogens Useful for PET

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REPORT DATE: July 1996

TYPE OF REPORT: Annual

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	July 1996	Annual (1 Jun 95 - 31 May 96)

4. TITLE AND SUBTITLE
New Approaches to the Labeling of Estrogens Useful for PET

5. FUNDING NUMBERS
DAMD17-94-J-4029

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, MD 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*

Estrogen receptor positive breast tumors are evaluated by positron emission tomography (PET) utilizing radiolabeled estrogen ligands. This imaging technique is used to predict the tumor's response to therapy and to follow the progress of disease.

Desiring to find new estrogens with high binding affinity for the estrogen receptor, we synthesized 16α-methoxy estradiol. This compound previously had not been isolated nor its binding affinity measured. Characterization has been achieved by ^{1}H and ^{13}C NMR as well as by low resolution and high resolution mass spectrometry. The synthesis was achieved by applying the chemistry of methyl hypofluorite to steroids. Optimization of reaction conditions has laid the foundation for future radiolabeling studies. Binding affinity of this compound for the estrogen receptor is currently being determined.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Positron Tomography, Estrogens, Progestins, Carbon-11, Receptor Ligands, Breast Cancer	17
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Stephanie D Johnson 6/28/96

PI - Signature Date

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New Approaches To The Labeling Of Estrogens Useful For PET

Introduction

Radiolabeled estrogens are used to evaluate receptor-positive breast tumors in order to predict responsiveness to therapy.[1] One such clinical radiopharmaceutical is [F-18]-16α-fluoroestradiol-17β (FES).[2-4] In order to probe the binding affinity of other estrogens substituted at the 16α-position, we desired to synthesize 16α-[C-11]methoxy-estradiol. Knowing that FES has a relative binding affinity (RBA) of 54 for the estrogen receptor (relative to estradiol),[5] it was presumed that the 16α-methoxy derivative should also exhibit an affinity for the estrogen receptor. This type of compound had previously been difficult to synthesize[6-9], therefore, a binding affinity had not been measured.

The advantages of using C-11 compared to F-18 include a decreased dose to the patient during imaging as well as to the chemist during preparation of the radiopharmaceutical. The 20.4 minute half-life of C-11 provides a challenge synthetically necessitating the chemistry be confined to a few synthetic steps post-incorporation. Additionally, the set of useful one carbon C-11 precursors is limited[10], therefore, the search for new synthons capable of incorporating C-11 on an appropriate time scale is ongoing.

The chemistry of methyl hypofluorite, MeOF, fits the criteria for such a synthon. It has been shown to react quickly with C-C double bonds[11] and various types of enol ethers. MeOF reacts with methyl enol ethers to rapidly yield the corresponding α-methoxy ketones.[12] In this report, MeOF is described as being the only source of the novel electrophilic methoxylium ion species "MeO^+". Methyl hypofluorite is generated in 0.10-0.15 M concentration in 10 minutes from passing F_2 gas (20% in Ne) through methanol in acetonitrile at -45 °C. Isolation and characterization has been achieved by Kol.[13]

With the help of MeOF, 16α-methoxyestradiol has been produced from 17-methyl enol ether-3-OTf-estrone. Reduction and deprotection provided the desired target molecule 16α-methoxyestradiol. This novel estrogen has been characterized by ^1H and ^{13}C NMR as well as by

low resolution and high resolution mass spectrometry. Binding affinity is currently being determined and upon good result, incorporation of carbon-11 will be achieved with no-carrier added [C-11]CH_3OF.[14]

Results and Discussion

Desiring to utilize the chemistry of methyl hypofluorite through reactions with steroids, we envisioned a synthetic route leading to 16α-methoxy estradiol (**6**). This novel estrogen would be used to probe the estrogen receptor's tolerance for a methoxy substituent at the 16 position. The multi-step synthesis of this estrogen proved challenging as solubility problems, solvent effects, and purification difficulties were all encountered.

Continual improvements in these areas allowed for the successful isolation and characterization of the desired 16α-methoxy estradiol. The synthetic route followed is shown in Scheme 1. The hydoxyl group on the A ring of the steroid was first protected by conversion to a triflate (**1**). The protected estrone was tranformed into the methyl enol ether (**3**) via the dimethyl ketal (**2**). Reaction of **3** with MeOF in acetonitrile and chloroform gave the 16-methoxy estrone in 29% yield. Replacement of methylene chloride as the solvent with radical scavenging chloroform gave a cleaner reaction with less side products caused by radical reactions with tertiary hydrogens on the steroidal skeleton.

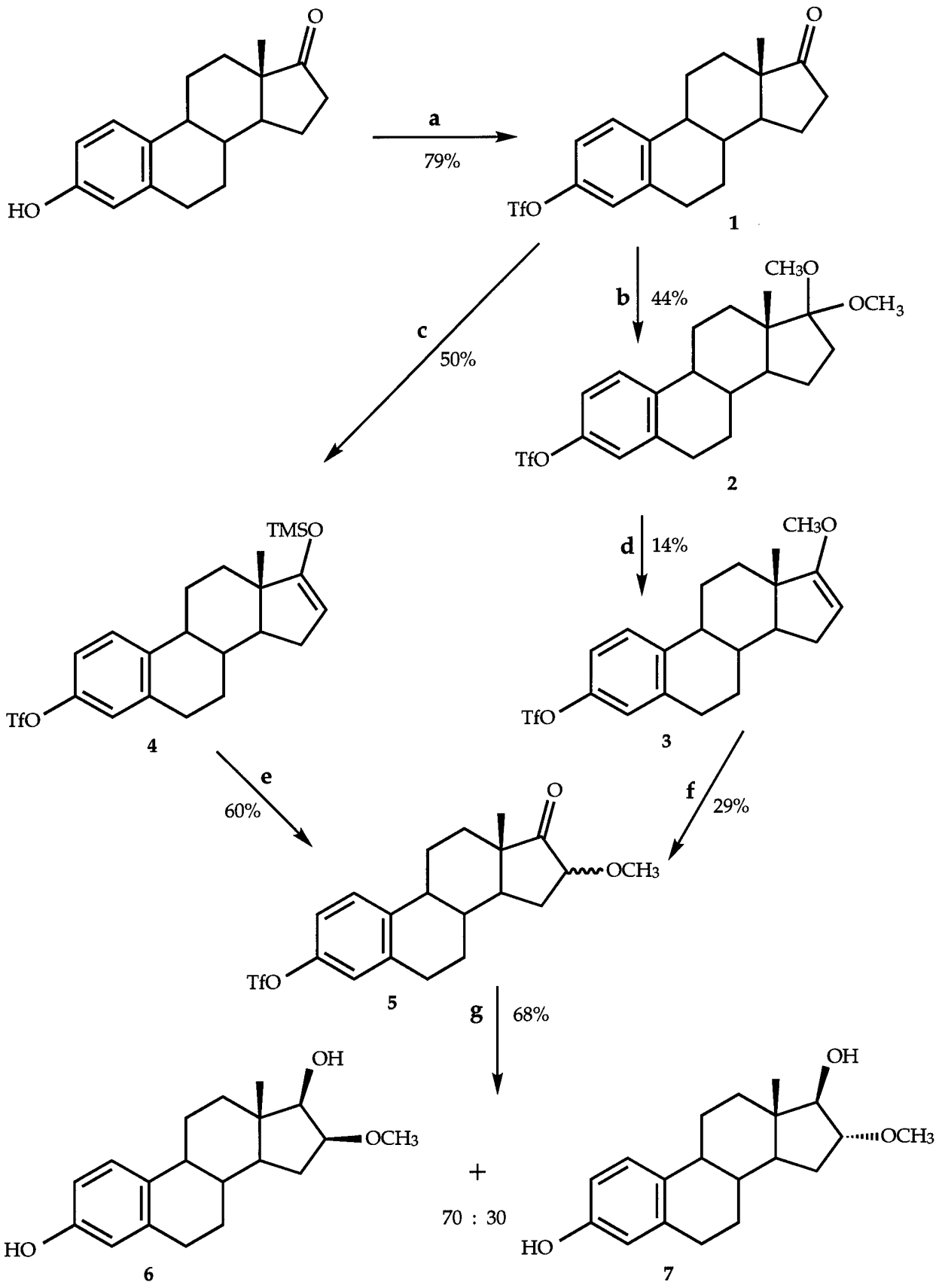
In previous studies, the yields for reactions with MeOF were quite low due to a solubility problem. Methyl hypofluorite is generated in acetonitrile at -45 °C, however, the steroidal substrates are not soluble at these conditions. This problem was solved by adding MeOF·ACN to the substrate dissolved in chloroform at 0 °C. Reversing the order of addition and changing the solvent from methylene chloride to chloroform successfully prevented precipitation.

Methyl enol ether substrates were suggested by Rozen to be the most promising functional group to react with MeOF.[12] The silyl enol ethers and enol acetates were found to be less promising. This observation focused our attention on the methyl enol ether triflate estrone (**3**) as the desired precursor. Difficulty was encountered in the preparation of **3**, as it was achieved in

low overall yield due to purification losses. The methyl enol ether is quick to decompose on silica hindering column purification. Basic alumina column purifications were tried to improve recovery, however, only a slight increase was seen. Separation on a Chromatotron gave the best results achieving decreased decomposition by a reduction in contact time with the silica plate and constant flow of nitrogen.

In order to produce larger quantities of the substrate to react with MeOF, the trimethylsilyl enol ether (TMSEE) (**4**) was synthesized. The TMSEE was thought to be less reactive than the MEE, however, it is achieved via a shorter synthetic route followed by a more facile purification. Production of larger quantities of substrate to react with MeOF outweighed the perceived lower reactivity. While testing the reaction of MeOF with **4**, NaF was added to the reaction in attempt to scavenge HF. In earlier reactions, an undesired product formed through addition of HF to the double bond. With the addition of NaF, this product was eliminated. The reaction of **4** with MeOF in radical scavenging chloroform, with modification of addition procedure to eliminate solubility problems, and with NaF to scavenge HF increased the purified yield of 16-methoxy triflate estrone to 60%. Thin layer chromatography of the crude reaction mixture showed the desired product with negligible side products.

The reaction of enol ether with MeOF leads to a mixture of the 16α-methoxy and the 16β-methoxy products. Both isomers can be seen by ^{1}H NMR as two singlet methoxy peaks: 3.40 ppm for 16α-OCH_3 and 3.41 ppm for 16β-OCH_3. Integration of these peaks shows the major product to be 16α (70%). Separation of these isomers is achieved by careful semi-preparative isocratic normal phase HPLC prior to reduction and deprotection. It is necessary to separate the isomers, for affinity to the estrogen receptor is directly affected by structural interferences.



Scheme 1. Synthetic route to 16-methoxy estradiol (**6**, **7**). **a**: 2,6-lutidine, Tf_2O, CH_2Cl_2, 30 min. **b**: $(CH_3O)_3CH$, CH_3OH, H_2SO_4, CH_2Cl_2, reflux, 48 hr. **c**: Et_3N, TMSCl, NaI, ACN, rt, 66hr. **d**: iPr_2EtN, TMSOTf, CH_2Cl_2, rt, 4 hr **e**: $CH_3OF \cdot ACN$, NaF, $CHCl_3$, -45 °C. **f**: $CH_3OF \cdot ACN$, $CHCl_3$, -45°C. **g**: 1) $LiAlH_4$, Et_2O, -78°C 2) HCl

Experimental

General. Materials were obtained from Fisher Scientific (St. Louis, MO) or Aldrich Chemical Co. (Milwaukee, WI) and used without further purification unless otherwise noted. Fluorine (20% in Neon) was purchased from Acetylene Gas (St. Louis, MO). Lutidine was distilled over BaO before use and CH_2Cl_2 was distilled from CaH_2. Organic extracts were concentrated under reduced pressure (aspirator) with the aid of a rotary evaporator. Melting points were obtained on a Electrothermal melting point apparatus and are reported uncorrected. Thin layer chromatography was analyzed on Whatman PE Sil G/UV 250 μm silica gel plastic backed plates. Purification by column chromatography was carried out with 70-230 mesh silica gel. Normal phase semi-preparative HPLC purification was accomplished on a Whatman Partisil 10 column. Fractions were analyzed for purity by normal phase analytical HPLC on an Alltech/Applied Science VersaPack Silica 100 300 mm long column. NMR spectra were obtained for ^1H and ^{13}C at 300 MHz on a Varian-Gemini spectrophotometer. Samples were dissolved in $CDCl_3$ with trimethylsilane as an internal standard. Chemical shifts (δ) are reported in parts per million.

3-trifluoromethanesulfonyloxy-estra-1,3,5(10)-triene-17-one (1).

Triflate estrone was prepared by the method of Kiesewetter.[15] Estrone (3.0 g, 11.10 mmol) was dissolved in 6 ml 2,6-lutidine and 75 ml CH_2Cl_2 and cooled in an ice/water bath. Triflic anhydride (2ml, 11.18 mmol) was added via syringe over 5 minutes. The red reaction mixture was stirred at 0 °C for 30 minutes and then quenched by addition of water. The aqueous and organic layers were separated and the organic phase was washed thrice with 0.4 M $CuSO_4$. The aqueous layers were back extracted with CH_2Cl_2 and the combined organic fractions were washed with brine. Upon drying over $MgSO_4$ and filtering, the organic solvent was removed under reduced pressure. Reaction progress was monitored by thin layer chromatography developed in 30% ethyl acetate/ 70% hexane. The desired product was visualized by UV or ethanolic $KMnO_4$ and found to be the major spot with rf=0.35. Reaction mixture was deposited on silica and subjected to flash column chromatography (30% ethyl acetate/ 70% hexane) providing

3-triflate estrone, **1**. Further purification by recrystallization from methanol provided a white crystalline solid in 79% yield (3.52g, 8.76 mmol). M.p.= 82-83 °C. NMR data as previously reported.[15]

17-dimethyl ketal-3-trifluoromethanesulfonyloxy-estrone (2).

The dimethyl ketal triflate estrone was prepared by a modified procedure from Gassman.[16] Triflate estrone , **1**, (5.02 g, 12.47 mmol, 1 equiv) was dissolved in trimethyl orthoformate (3.04 ml, 27.8 mmol, 2.23 equiv) and methanol (1.3 ml, 0.1 ml/mmol ketone) with stirring. The reaction mixture was cooled to 0 °C in an ice/water bath and 2 µl concentrated H_2SO_4 (0.072 mmol, 5.8 mequiv) was added as an acid catalyst. The solution was refluxed for two days. Upon refluxation, the solution changed from colorless to dark orange and became very viscous. Methylene chloride was added before the solution was cooled in order to decrease viscosity. The reaction mixture was neutralized with addition of freshly prepared methanolic sodium methoxide. The mixture was further diluted with CH_2Cl_2 and water. The layers were separated and the organic layer was extracted by washing thrice with water and once with brine. The aqueous layer was back extracted with CH_2Cl_2 and the organic fractions were combined, dried over $MgSO_4$, filtered, and solvent removed under reduced pressure. Reaction products were monitored by thin layer chromatography, developed in 20% ethyl acetate/ 80% hexane and visualized by UV or ethanolic $KMnO_4$. Two major products were visualized at rf= 0.54 and 0.40. The more lipophilic product was 17-methyl enol ether triflate estrone , **3**, and the less lipophilic product was the intended dimethyl ketal. The reaction mixture was purified on a Chromatotron using a 2 mm UV activated silica plate with 2.5% ethyl acetate/ 97.5% hexane as the eluent. Separation of the mixture into five aliquots was necessary in order to stay within the capacity of the plate. Methyl enol ether (MEE) was obtained in 12% yield (0.611 g, 1.47 mmol); the dimethyl ketal in 44% yield (2.43 g, 5.42 mmol). ^1H NMR: d 0.92 (s, 3, 18-CH_3), 1.2-3.0 (m, 15), 3.25 (d, 6), 7.00 (m, 2, Ar), 7.33 (d, 1, Ar).

17-methyl enol ether-3-trifluoromethanesulfonyloxy-estrone (3).

The methyl enol ether triflate estrone was prepared by a modified procedure from Gassman.[16] A 25 ml flask was charged with the dimethyl ketal, **2**, (1.447 mmol, 0.649 g), CH_2Cl_2 (7 ml), and diisopropyethylamine (305 µl, 1.75 mmol, 1.21 equiv) and kept stirring under N_2. The solution was cooled to -20 °C in a methanol/dry ice bath before addition of TMSOTf (308 µl, 1.59 mmol, 1.1 equiv) dropwise via a syringe. The reaction mixture was allowed to warm to room temperature. After stirring for 4 hours, the reaction was quenched by addition of 0.1 equiv NaOH. Mixture was stirred vigorously for ca. 1 minute, diluted with 5-10 ml pentane, and refrigerated overnight to precipitate the trialkylammonium triflate salt. Separation of the liquid from the salt was achieved by vacuum filtration. Crystals were washed with cold pentane. Filtrate was washed with brine once and dried over $MgSO_4$. Filtration and removal of solvent provided a mixture of starting material and the desired methyl enol ether. Purification was accomplished on a Chromatotron with a 2 mm UV activated silica plate and 5% ethyl acetate/ 95% hexane as the eluent. The methyl enol ether was obtained in 14% yield (81 mg, 0.195 mmol). ^{1}H NMR: 0.90 (s, 3, 18-CH_3), 1.25-2.4 (m, 11), 2.91 (m, 2), 3.61 (s, 3, OCH_3), 4.39 (m, 1, =C-H), 6.97-7.03 (m, 2, Ar), 7.32 (d, 1, Ar). MS (FAB, NBA matrix) MH^+ 417. HRMS (MH^+): 417.1346 and 417.1351, $C_{20}H_{23}O_4F_3S$ requires 417.1347.

3-trifluoromethanesulfonyloxy-17-[(trimethylsilyl)oxy]estrone (4).

Procedure adapted from Cazeau .[17] Triflate estrone, **1**, (0.5139 g, 1.28 mmol), freshly distilled triethylamine (221 µl, 1.59 mmol, 1.24 equiv), and freshly distilled trimethylchlorosilane (201 µl, 1.59 mmol, 1.24 equiv) were combined in order in a 50 ml flask under N_2. A white slurry was produced. Dried NaI (0.238 g, 1.59 mmol, 1.24 equiv) in 1.6 ml anhydrous acetonitrile was added dropwise to the slurry. Slight white smoking was observed with the addition of each drop. Reaction was stirred for ca. 66 hours and then diluted with cold hexane and ice water. The separated organic layer was washed thrice with cold saturated $NaHCO_3$. The aqueous extracts were back extracted two times with hexane. Combined organic fractions were

dried over $MgSO_4$, filtered, and solvent removed under reduced pressure. Purified by silica flash column chromatography (10% ethyl acetate/ 90% hexane). Silyl enol ether was obtained in 50% yield (0.304 g, 0.64 mmol). M.p.= 84-88 °C. ^1H NMR: 0.21 (s, 9, TMS), 0.88 (s, 3, 18-CH_3), 0.97-2.1 (m, 11), 2.35-2.40 (m, 2), 4.55 (m, 1, =C-H), 6.72-6.82 (m, 3, Ar).

16-methoxy-3-(trifluoromethanesulfonyloxy)estrone (5).

Reaction with methylenol ether: 25 ml anhydrous acetonitrile and 1 ml anhydrous methanol were added to a N_2 swept flask. Solution was cooled to -45 °C in a dry ice/acetonitrile bath. Fluorine gas (20% in Neon) was bubbled into the solution for 30 minutes. Bubbling was stopped and an aliquot of the mixture was removed, diluted with 25 ml water, and titrated with thiosulfate in the presence of excess iodide. The color changes from yellow to colorless at the equivalence point. Titration determined the solution to contain 2.23 mmol of methyl hypofluorite (0.8715 M). The methyl enol ether, **3**, (0.100 g, 0.240 mmol) was dissolved in $CHCl_3$ (5 ml) in a separate flask and cooled to 0 °C. Methyl hypofluorite·ACN solution was poured into the substrate flask. The mixture was stirred at 0 °C for 5 minutes followed by warming to RT over 30 minutes. Reaction was quenched by addition of 250 ml saturated $NaHCO_3$. Aqueous phase was extracted with chloroform thrice and organic layer was washed once with brine. Combined organic fractions were dried over $MgSO_4$, filtered, and solvent removed under reduced pressure. Purification by silica flash column chromatography (15% ethyl acetate/ 85% hexane). The 16α/β product was obtained in 29% yield (30 mg, 0.068 mmol).

Reaction with trimethylsilylenol ether: 48 ml anhydrous acetonitrile and 2 ml anhydrous methanol were added to a N_2 swept flask. Solution was cooled to -45 °C in a dry ice/acetonitrile bath. Fluorine gas (20% in Neon) was bubbled into the solution for 35 minutes. Titration determined the solution to contain 5.11 mmol of methyl hypofluorite (0.105 M). The silyl enol ether, **4**, (0.330 g, 0.695 mmol) was dissolved in $CHCl_3$ (10 ml) in a separate flask and cooled to 0 °C. NaF (0.030 g) was added to the methyl hypofluorite solution to scavenge HF.

The solution sat for ca. 30 seconds before being poured into the substrate flask. The mixture was stirred at 0 °C for ca. 5 minutes followed by warming to RT over 40 minutes. Reaction was quenched by addition of 250 ml saturated $NaHCO_3$. Aqueous phase was extracted with chloroform thrice and organic layer was washed once with brine. Combined organic fractions were dried over $MgSO_4$, filtered, and solvent removed under reduced pressure. Purification by silica flash column chromatography (15% ethyl acetate/ 85% hexane). The 16α/β mixture was obtained in 60% yield (30 mg, 0.068 mmol).

^1H NMR: 0.96 (s, 3, 18-CH_3), 1.4-2.6 (m, 11), 2.93-2.96 (m, 2), 3.53 (s, 3, 16α-OCH_3) [3.54 (s, 3, 16β-OCH_3)], 3.97 (d, 1), 7.00-7.05 (m, 2, Ar), 7.34 (d, 1, Ar). ^{13}C NMR: 14.44, 25.38, 25.90, 28.92, 29.33, 29.38, 31.39, 35.79, 37.57, 43.93, 47.73, 58.72, 79.68, 118.3, 121.2, 127.1, 139.2, 140.1, 147.58, 189.2, 216.6. ^{19}F NMR: (internal reference: $CFCl_3$) -73.5 (16α), -73.4 (16β). MS (FAB, NBA matrix) MH^+ 433. HRMS (MH^+): 433.1301 and 433.1300, $C_{20}H_{23}O_5F_3S$ requires 433.1296.

16-methoxy estradiol-17β (6, 7).

Methoxy triflate estrone, **5**, (18.4 mg, 0.0425 mmol) was dissolved in freshly distilled diethyl ether (3.0 ml) under N_2. The solution was cooled to -78 °C while stirring in a dry ice/isopropanol bath. $LiAlH_4$ (1.2 ml, 1.0 M) was added dropwise over ca. 2 minutes. The reaction was stirred at -78 °C for 22 minutes, a pale yellow color, followed by warming to RT over 22 minutes resulting in a cloudy white solution. Reaction was quenched with HCl (2.4 ml, 6 N). Aqueous layer was extracted thrice with ether. The organic fractions were passed through a $MgSO_4$ column and a 0.22 μ filter. Solvent was removed under reduced pressure. Purification by semi-preparative normal phase HPLC (40% (1:19 isopropanol: CH_2Cl_2)/ 60% hexane). The final product was obtained in 68% yield (8.8 mg, 0.0291 mmol). ^1H NMR: 0.71(s, 3, 18-CH_3), 1.25-2.4 (m, 11), 2.79-2.84 (m, 2), 2.88 (d, 1), 3.40 (s, 3, 16α-OCH_3) [3.41(s, 3, 16β-OCH_3)], 3.75-3.77 (dd, 1), 3.95-4.10 (m, 1), 4.82 (br s, 1), 6.55-6.65 (m, 2, Ar), 7.16 (d, 1, Ar). ^{13}C NMR: 16.98, 25.73, 27.99, 29.68, 31.25, 31.63, 38.72, 43.50, 46.19, 58.04, 77.30, 81.55,

112.64, 115.19, 126.51. MS (FAB, NBA matrix) M^+ 302. HRMS (M^+): 302.1883 and 302.1892, $C_{19}H_{26}O_3$ requires 302.1882.

Conclusion

The estrogen analogue with a 16α-methoxy substitution has been isolated and characterized. The methyl hypofluorite reaction conditions have been optimized to increase the yield of the 16-methoxy estradiol. An increase in yield was attributed to changing the solvent from methylene chloride to radical scavenging chloroform, addition of NaF to the reaction to scavenge HF, and modification of substrate addition to prevent precipitation of the steroid.

Binding affinity of the methoxy estradiol is currently being accessed. With result of a favorable binding affinity for the estrogen receptor, radiolabeling studies of the methoxy estradiol with carbon-11, utilizing [C-11]MeOF, will be instigated. Radiolabeling of the compound will allow for evaluation in an animal model to determine uptake into estrogen receptor rich tissues. These models are used to predict the effectiveness of a compound for imaging estrogen receptor positive breast tumors.

This research project has conformed to the schedule outlined in the statement of work.

Time Line for Statement of Work

Goal	Year of Funding 0	1	2	3	4
1) Complete Required Course Work		---------->			
		..........>complete			
2) Synthesize Authentic Non-Radioactive Compounds		----------	----------	---------->	
	.....				
3) Measure Binding Affinity of Non-Radioactive Compounds			---------->		
			...		
4) Synthesize Radioactive Compounds				-------->	
5) Evaluate Best Compounds in Animal Models				---------->	
6) Write Thesis				--->	

---------->	represents original time estimate
..........>	represents work completed

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